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Diagnostic and Treatment Response Imaging in Lymphomas

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1. Introduction

The lymphomas are a heterogeneous group of malignant diseases, which vary with respect to their molecular features, genetics, clinical presentations, treatment approaches and outcomes. They are divided into two broad groups on the basis of pathology: Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). They comprise approximately 5% - 6% of all malignancies and are the fifth most frequently occurring type of cancer in the Western world (Jemal A *et al*., 2009). HD and many histological sub-types of NHL are potentially curable with appropriate chemotherapy and/or involved-field radiotherapy, and patients with disease relapse may be cured by second-line salvage treatments (Hampson FA and AS Shaw, 2008). Accurate staging and response assessment are essential to guide treatment decisions. Molecular imaging has become an essential tool in the early diagnosis (guiding biopsy), initial staging and risk stratification, monitoring response to therapy, and detection tumor recurrence of lymphomas. Research in molecular imaging is also contributing to our understanding of the disease pathogenesis of lymphomas and helping to direct more effective care of patients with the diseases.

Computed tomography (CT) once was the single imaging modality for staging and monitoring morphological changes after treatment. The relatively recent integration of positron emission tomography (PET) with the use of [18]F-fluorodeoxyglucose tracer (^{18}F-FDG) into oncologic imaging has further improved baseline staging and facilitated functional evaluation of disease behaviour (such as tumor malignancy grade), metabolic response to therapy, and earlier detection of disease recurrence (Ngeow JY *et al*., 2009; Schoder H *et al*., 2005; Spaepen K *et al*., 2002). Particularly for conclusions of therapy response assessment, FDG-PET has been shown to be considerably more accurate than anatomical imaging by CT because of its ability to distinguish between viable tumor and necrosis or fibrosis in post-therapy residual masses.

The specificity of FDG-PET is improved with the addition of CT. Integrated PET/CT, with the advantage of combining functional and anatomical information and better attenuation correction, is regarded to be the current standard of practice for the management of

lymphomas. However, PET/CT is expensive, time-consuming, involves exposure to ionizing radiation, and is not widely available because it requires support infrastructure, such as cyclotrons and radiochemistry laboratories (Huang B *et al*., 2009). In contrast, magnetic resonance imaging (MRI) provides excellent tissue contrast and high spatial resolution, and lack of ionizing radiation. It may be a potential alternative for the surveillance of lymphoma patients with multiple follow-up examinations. Moreover, the rapidly evolving parallel imaging acquisition technique with multi-channel phased array surface coils has enabled a high spatial resolution whole-body MR examination within a reasonable time (Lauenstein TC and RC Semelka, 2006). The development of imaging modalities, which can encompass the entire body, is of great importance, especially for aggressive lymphomas, in which extensive disease involvement is common (Antoch G *et al*., 2003; Ghanem N *et al*., 2006).

Whole-body MRI has shown advantages for the detection of distant metastatic diseases, especially from tumors frequently spreading to the brain, liver, or bone marrow (Kwee TC *et al*., 2009), and it has been introduced as a whole-body bone marrow screening application (Schmidt GP *et al*., 2009). Within this context, whole-body MRI is highly accurate for staging of hematologic diseases, such as lymphomas. However, additional bone marrow biopsy is still considered mandatory.

Evaluation of nodal disease by CT and conventional MRI still relies on size criteria, lymph nodes with a short-axis diameter greater than 10 mm are generally considered positive. However, lymph nodes may be enlarged reactively and even small lymph nodes may be infiltrated by malignant cells. Thus, tumor in unenlarged lymph nodes may go undetected. Diffusion-weighted MRI (DWI) is a noninvasive technique that probes the random microscopic motion of water molecules *in vivo* (Le Bihan D, 1995). DWI with apparent diffusion coefficient (ADC) mapping provides quantitative physiological and functional information regarding characterization of lymphomas. Because of their high cellularity and high nuclear-to-cytoplasm ratio, aggressive lymphomas have relatively high signal intensity on DW images and low ADC values (Sumi M *et al*., 2007). Recent studies have shown that DWI with ADC mapping could distinguish between benign and malignant lymphadenopathy (Holzapfel K *et al*., 2009; Perrone A *et al*., 2009), and it may have prognostic potential in patients with aggressive lymphomas (Wu X, PL Kellokumpu-Lehtinen *et al*., 2011). An advantage of DWI over conventional MRI sequences in the evaluation of lymphoma is the high lesion-to-background contrast, which make it a valuable imaging modality for detecting metastasis and cancer relapse, and it has also been used to assess treatment response in various malignancies including lymphomas (Wu X, PL Kellokumpu-Lehtinen *et al.,* 2011). Our recent pilot study showed that DWI, in combination with whole-body MRI, yielded results comparable with those from integrated PET/CT in treatment evaluation of patients with diffuse large B-cell lymphoma (Wu X, PL Kellokumpu-Lehtinen *et al.,* 2011). DWI and PET/CT share similar applications in the field of clinical oncology. This is important when a patient is not suitable for PET/CT exams (e.g. diabetes) or PET/CT is not available.

This chapter will highlight the most important and potential applications of FDG-PET/CT and MRI including whole-body MRI and DWI emphasizing the strengths and pitfalls of each imaging approach in diagnosis, initial staging, and response assessment of lymphomas.

2. Classification of malignant lymphomas

The lymphoproliferative disorders encompass a collection of lymphoid neoplasms with different clinical and histological presentations. The classification of lymphoid malignant diseases has been beset by difficulties. In 1994, a census for universal lymphoma classification was published in the form of the Revised European-American Lymphoma (REAL) classification (Harris NL *et al*., 1994). The current World Health Organization (WHO) classification was derived from the REAL criteria, in which NHL is categorized into more than 20 subtypes on the basis of cell origin (B- or T-cell precursor), morphological, and immunophenotypic data (Harris NL *et al*., 2000). Diffuse large B-cell lymphoma and follicular lymphoma account for more than 50% of cases of NHL. The WHO classification helps to determine not only malignancy grade, but also prognosis. Systems in which NHL is grouped into indolent, aggressive, and very aggressive disorders are practically very useful (Cronin CG *et al*., 2010).

3. Diagnosis, initial staging, and prognosis assessment of malignant lymphomas

Diagnosis is based on an integration of morphological (lymph nodes, blood and bone marrow), immunophenotypic, molecular, cytogenetic data, and clinical behavior. Many lymphomas have characteristic morphological features, but no specific biomarker is of diagnostic value. In patients suspected of malignant lymphoma, a surgical excision biopsy of an enlarged lymph node (or extra-nodal site) is mandatory to confirm the diagnosis and to define the histological subtypes.

Once the diagnosis of HD or NHL has been established by biopsy of a particular site, accurate determination of disease extent (staging) is crucial for appropriate treatment planning and prognosis prediction. In addition, knowing the sites of involvement at time of diagnosis makes it possible to accurately restage at the end of therapy and document a complete remission. Conventional staging techniques, considered the standard reference, include contrast-enhanced CT of the neck, chest, abdomen and pelvis, uni/bilateral bone marrow biopsy, and in some cases MRI. CT has been the most commonly used imaging modality for initial staging of lymphomas for decades. In patients with aggressive NHL and HD, FDG-PET and FDG-PET/CT are increasingly applied for the initial staging. Bone marrow biopsy is an invasive procedure and can be subject to sampling errors (Pelosi E *et al*., 2008). Therefore, PET scan should be the first step in lymphoma staging workup so that it could be used to guide bone marrow biopsy in the presence of patchy bone marrow lesion (Figure 1). The role of FDG-PET in indolent lymphoma is still unclear, and not all indolent lymphomas are FDG-avid. In current clinical practice, the use of MRI for staging malignant lymphoma is still limited. It is mainly applied as an adjunct to CT in selected cases with soft tissue lesions, or suspected involvement of the central nervous system or bone marrow that need to be further evaluated (Vermoolen MA *et al*., 2011).

Staging of both HD and NHL is based on the Ann Arbor classification, with the inclusion of a definition of bulky disease known as the Cotswold modification (Lister TA *et al*., 1989). This staging system encompasses the number of sites of disease involved, the type of involvement (nodal or extra-nodal), and the distribution of disease. Whole-body imaging is

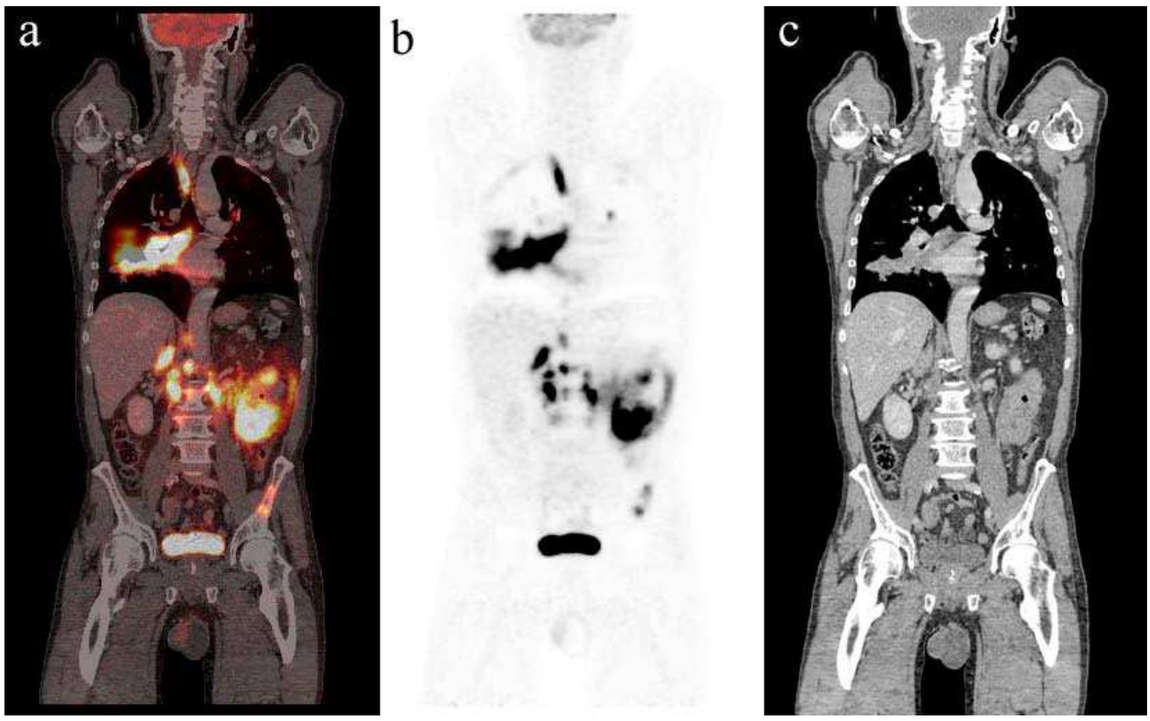

Fig. 1. A coronal slice of fused PET/CT image (a), the corresponding PET image (b) and CT image (c) in a 62-year-old male patient with diffuse large B-cell lymphoma
Multiple FDG avid lesions are showing in the cervical, mediastinum, abdominal region, and the left iliac on both the fused PET/CT image and the PET image. The iliac lesion was neither detected by the corresponding CT image, nor by bone marrow biopsy that was performed at the right side of the iliac.

therefore an indispensable tool. Ann Arbor stage I: Only one lymph node region or extra-nodal site is affected. Stage II: Multiple lymph node regions are affected, but limited to the same side of the diaphragm. Stage III: Involvement of lymph node regions on both sides of the diaphragm, which may be accompanied by local extra-nodal extension. Stage IV: Diffuse involvement of one or more extra-nodal organs or sites, including bone marrow, liver, and lung (Lister TA *et al.*, 1989). Accurate staging is critical for identifying patients with early stage (stage I or II) lymphoma, some of which might be treated with involved-field radiation therapy. Chemotherapy is performed in patients with more advanced stage disease (stage III or IV).

The International Prognostic Score (IPS) based on seven factors consisting of serum albumin, hemoglobin, gender, stage, age, leukocytosis, and lymphocytopenia is used for newly diagnosed HD patients. Whereas the International Prognostic Index (IPI) is the most widely used prognostic index for adult NHL, which is based on both clinical and imaging findings including age, serum lactate dehydrogenase (LDH) level, extent of disease, and performance status. The IPI is derived from an additive score of 0 to 5 points to stratify patients as having low (0 - 1 point), low-to-intermediate (2 points), high-to-intermediate (3 points), or high (4 - 5 points) prognostic risk (Shipp MA, 1994). However, considerable variations still remain in

the outcome of individual patients within the same prognostic group because of the biological and clinical heterogeneity of the diseases. Currently, the paradigm of treatment in HD and NHL is moving towards a more risk-adapted therapy based on the individual patient's prognosis by advanced imaging techniques.

4. Response assessment of malignant lymphomas

The response to therapy of lymphomas shows a high variability, therefore, it is important to have knowledge of early chemotherapy efficacy for individual patient. Furthermore, assessment of early- or mid-treatment response to chemotherapy has been shown to be of prognostic value in patients with malignant lymphomas (MacManus MP *et al*., 2007). Identification of nonresponders at an early stage allows for the adjustment of chemotherapy and radiotherapy regimens promptly and thereby may improve the outcomes and decrease the toxicity and costs that associated with ineffective treatment. However, the value of altering therapy based on early- or mid-treatment FDG-PET remains to be established (Cheson BD *et al*., 2007). Response assessment at the end of treatment is performed to assess whether there is a partial or complete remission, which is important for determining the need for additional treatment and for determining prognosis. The International Working Group (IWG) criteria, published in 1999, have become the widely accepted standard for response assessment in NHL, and were subsequently adopted for HD (Cheson BD *et al*., 1999). Although based primarily on CT findings, the IWG criteria take bone marrow biopsy, clinical, and biochemical information into account. The IWG criteria have proved extremely useful in the standardization of treatment response, but they do have a number of limitations. As a consequence of this, together with advances in functional imaging, revised criteria that incorporate both CT and FDG-PET were published in 2007 (Cheson BD *et al*., 2007). Complete remission indicates disappearance of all evidence of disease, partial remission indicates regression of measurable disease and no new sites, stable disease indicates failure to attain complete remission or partial remission, and progressive disease indicates the appearance of new lesions or increase by ≥50% of previously involved sites (Cheson BD *et al*., 2007). According to the revised criteria, a patient is considered to be complete remission even if a residual CT mass is present, provided the mass has changed from being FDG avid or PET-positive to PET-negative.

5. Different imaging modalities

5.1 Computed tomography

The introduction of CT in the mid 1970s was a tremendous breakthrough in noninvasive imaging, and its potential for staging malignant lymphoma was soon recognized and investigated. Since then, CT has gradually become the imaging modality of choice for staging malignant lymphomas. CT technology has continuously been developed and refined; major milestones include the introduction of spiral (helical) CT, and the advent of multi-detector row CT that increases the speed of data collection dramatically. In addition, current CT scanners have a faster gantry rotation. These properties enable acquisition of high resolution cross-sectional images of the whole-body within only a couple of seconds, which minimizes or eliminates breathing artifacts (Kwee TC, Kwee RM *et al*., 2008; Rydberg J *et al*., 2000). As a result, lymph nodes of 5 mm or less in diameter can be detected. In

combination with powered injectors for rapid bolus administration of intravenous contrast medium, focal extra-nodal lesions on the order of a few millimeters can be identified (Lucey BC *et al*., 2005; Vinnicombe SJ and RH Reznek, 2003). Intravenous contrast medium facilitates nodal recognition in the neck and in the retroperitoneum in patients with a paucity of adipose tissue. The importance of adequate bowel opacification with dilute oral contrast (so as to avoid confusion with intra-abdominal and pelvic masses) was well recognised (Kwee TC, Kwee RM *et al*., 2008). However, contrast-enhanced CT is not very helpful in differentiating normal from malignant lymph nodes. CT has limitations in differentiating malignant from benign small lymph nodes or, after treatment, neoplastic tissue from fibrosis.

CT remains the basic imaging modality for initial staging malignant lymphomas because of its widespread availability and relatively low cost. However, the limited specificity of CT is still a fundamental problem in oncology, e.g. to detect pathological changes in normal-sized structures, to detect lesions that have poor contrast with surrounding tissue. At initial staging, determination of nodal involvement by CT is based on size criteria. Lymph nodes viewed on CT are considered as pathological if the maximum allowed long-axis diameter of 15 mm is exceeded, and/or if the short-axis diameter is more than 10 mm. In addition, nodal involvement is presumed if clustering of normal-sized lymph nodes is present in the anterior mediastinum or mesentery, or if lymph nodes of any size are visualized in areas where they normally are not observed (Vermoolen MA *et al.,* 2011). CT evaluation on the basis of nodal size has historically been regarded as the reference standard imaging technique for staging, with a reported sensitivity and specificity for nodal disease of 87.5% and 85.6%, respectively (la Fougere C *et al*., 2006). General criteria for extra-nodal involvement are any focal density alterations or mass lesions involving soft tissues, bones, parenchymal organs and serosal cavities (Vermoolen MA *et al.,* 2011). Comparing current with previous CT scans may improve diagnostic reliability. Nevertheless, the use of CT alone in restaging malignant lymphoma can be limited, since it is not able to differentiate residual viable tumor tissue from therapy-induced fibrosis. Following treatment of lymphoma by chemotherapy and/or radiation, up to 40% of patients with nodal disease have a residual mass on CT. Previous studies have shown that only 10 - 20% of such patients will have disease in these residual masses (Hampson FA and AS Shaw, 2008). In early response assessment, CT is not an ideal diagnostic tool, as morphological changes may lag behind rapid functional changes in response to therapy. Another weakness of CT is the limited sensitivity for detecting bone marrow involvement, which, if present, by definition indicates stage IV disease (Vinnicombe SJ and RH Reznek, 2003) (Figure 1).

Major disadvantages of CT are exposure of the patient to ionizing radiation and the administration of iodinated contrast agents, which may induce secondary cancers and cause allergic reactions, respectively (Kwee TC *et al*., 2009). Nevertheless, contrast-enhanced diagnostic CT remains the base for initial measurements of involved sites and detection of complications such as adjacent organ compression, although combined FDG-PET/CT is increasingly applied for initial staging of malignant lymphomas.

5.2 FDG-PET

Positron emission tomography was developed in the 1970s soon after CT (Phelps ME *et al*., 1975). It is based on the use of positron-emitting radiopharmaceuticals and the detection in

coincidence of the 2 nearly collinear 511 keV photons emitted following positron annihilation with an electron. Fluorodeoxyglucose (FDG), an analogue of glucose; is taken up by high-glucose-using cells. After transport into tumour cells, ^{18}F-FDG is phosphorylated to ^{18}F-FDG-6-phosphate that cannot be further metabolised. It will take approximately 60 minutes for the radiotracer to travel through the body and to be absorbed by the organ or tissue being studied. Thus, 60 minutes after intravenous injection, the concentrations of ^{18}F-FDG tracer give tissue glucose metabolic activity, in terms of regional glucose uptake. Cancer imaging by ^{18}F-FDG-PET is based on the observation that most cancers, including many lymphomas, metabolize glucose at an abnormally high rate (Warburg O, 1956). The most aggressive tumors require greater glucose consumption to maintain their accelerated growth. Imaging of malignant lymphoma with FDG was first described in the 1980s (Paul R, 1987), and the first reports on FDG-PET as a whole-body staging method in malignant lymphoma was published in the 1990s (Moog F *et al*., 1997). PET technology has improved dramatically since its development. Initial patient imaging units had a system resolution greater than 15 mm, whereas current units have a 4 to 5 mm resolution. Raw data should be reconstructed by means of iterative expectation maximization algorithms, which provide superior signal-to-noise ratio compared with filtered back-projection images (Kwee TC, Kwee RM *et al.*, 2008). When one (or both) of the annihilation photos scatters in the body, it is prevented to be detected appropriately, which is called attenuation. Attenuation effects produce regional nonuniformities, distortions of intense structures, and edge effects. To improve anatomical delineation, additional transmission scanning for attenuation correction using an external radiation source is required. Attenuation correction also allows for semiquantitative evaluation, which offers a more objective way to assess FDG uptake. Nonattenuation corrected images should also be evaluated, because the attenuation correction itself may also introduce image artifacts (Rohren EM *et al*., 2004).

FDG-PET imaging protocols vary from institution to institution, which highlights the need for standardization. In the most frequently used protocol, patients fast for 4 - 6 hours prior to the injection of FDG. Imaging commences approximately 60 minutes after the injection of a typical FDG dose of 370 MBq. Serum glucose levels of less than 150 mg/dl are desirable. Patients are also instructed to avoid any kind of strenuous activity prior to the examination and following injection of the radioisotope to avoid physiological muscle uptake of FDG.

Visual analysis of an FDG-PET scan can characterize the intensity of metabolic activity as low, moderate or high. In many cases visual image interpretation is sufficient to identify malignant lesions. Any focus of visually elevated FDG uptake relative to the background (surrounding normal tissue), not located in areas of physiologically increased uptake, is regarded as positive for malignant lymphomas (Vermoolen MA *et al.,* 2011). In organs with physiological FDG uptake (e.g., spleen and liver), focal or inhomogeneous uptake patterns are considered to be indicative of malignant lymphoma (Figure 1). Nevertheless, quantitative analysis of FDG uptake may complement visual image interpretation because it provides objective criteria, thus minimizing interobserver variability in image interpretation. The FDG uptake can also be assessed semiquantitatively using the standardized uptake value (SUV). The standardized uptake value, an index of glucose metabolism on FDG-PET image, is the ratio between the measured and expected uptake if FDG were distributed evenly throughout the body. The maximum standardized uptake value (SUVmax) has been used in daily clinical setting to evaluate the degree of malignancy,

metabolic response to therapy, and early detection of disease recurrence (Ngeow JY *et al*., 2009; Schoder H *et al*., 2005; Spaepen K *et al*., 2002; Wu X, P Dastidar *et al*., 2011). Measurements of metabolic burden, which incorporate both FDG uptake and PET lesion volume may prove more useful for risk stratification and response assessment (Berkowitz A *et al*., 2008).

Owing to its high diagnostic accuracy, FDG-PET has become an established imaging modality in addition to CT for the initial staging, response assessment, and detection recurrence of lymphomas [4]. Previous studies have demonstrated that FDG-PET is superior to CT in staging HD and high-grade NHL, with sensitivity, specificity, and accuracy reported at 85 - 98% (Hampson FA and AS Shaw, 2008; la Fougere C *et al*., 2006). As a consequence a significant number of patients will have a change of stage, with many of these having their management revised (Hampson FA and AS Shaw, 2008). Most commonly this results in the disease being upstaged, since patients with true early stage disease are differentiated by FDG-PET from those with otherwise occult advanced disease.

FDG-PET is useful in lymphoma classification or grading, as well as guiding biopsy. Several studies have shown that standardized uptake value correlates with the degree of malignancy in lymphomas, and in patients with NHL and an standardized uptake value greater than 10 are quite likely to have aggressive disease (Okada M *et al*., 2010). The degree of FDG uptake by lymphoma cells may be a biomarker for disease biology: e.g. different histopathological subtypes of HD who have exhibited significantly different levels of FDG uptake (Hutchings M *et al*., 2006). Similarly, grade III follicular lymphomas appear to have significantly higher FDG uptake than grade I or II follicular lymphomas (Tang B *et al*., 2009). FDG uptake is lower in indolent lymphoma compared to aggressive lymphoma. Histological transformation of indolent lymphoma occurs in 20 – 30% of the patients. Recent study has shown that FDG-PET can be used as an accurate guide for biopsies in suspected transformed tissues (Bodet-Milin C *et al*., 2008). The standardized uptake value varies considerably in different tumors of the same lymphoma patients, and biopsies should be performed in the site with the maximum standardized uptake value of the whole body (the highest malignancy) that represents the malignancy of the disease (Bodet-Milin C *et al*., 2008; Wu X, P Korkola *et al*., 2011). However, histological analysis remains the gold standard to confirm the transformation, since there is considerable overlap in the range of maximum standardized uptake values for different subtypes of lymphomas.

The main advantage of FDG-PET over anatomical imaging techniques, such as CT, is its ability to detect metabolic changes in malignant lymphoma lesions before structural changes become visible. A pretreatment FDG-PET scan may identify additional focal bone marrow lesions that would be missed by bone marrow biopsy or CT examination (Figure 1). Furthermore, FDG-PET surpasses CT in differentiating residual viable tumor tissue from therapy-induced fibrosis, and this allows PET performed at the end of treatment to provide a more accurate response classification than assessment by CT. Therefore, when FDG-PET results are used to make treatment decisions at initial staging and response assessment, outcome may improve, particularly in patients with HD and aggressive NHL. In addition, early- and mid-treatment PET studies have been shown to be a good predictor of progression-free survival and overall survival. However, the value of FDG-PET for staging certain indolent NHLs that are not FDG-avid may be limited, and CT imaging remains the modality of choice in these subgroups (Vermoolen MA *et al*., 2011). Routinely, FDG avid

malignant lymphomas (HD, diffuse large B-cell lymphoma, follicular lymphoma, and mantle cell lymphoma) are well visualized both in initial staging and restaging. However, some subtypes of NHL, predominantly low-grade lymphomas, may have low or even no uptake of FDG. Nodal and extra-nodal marginal zone lymphomas, small lymphocytic lymphomas, primary duodenal follicular lymphoma, cutaneous T-cell lymphomas, and peripheral T-cell lymphomas all have been reported to be possibly FDG negative (Kwee TC, Kwee RM *et al.*, 2008). Caution is warranted in these histological subtypes of NHL because a negative FDG-PET scan could not rule out malignant lesions. It is also considered mandatory to perform a pretreatment FDG-PET scan in these variable FDG avid NHLs, since comparison of a post-treatment FDG-PET scan to a pretreatment FDG-PET scan will lead to more accurate restaging (Kwee TC, Kwee RM *et al.*, 2008).

A major drawback of FDG-PET is its lack of detailed anatomical information, which impedes precise localization of sites with FDG uptake. In addition, FDG-PET is not cancer specific; there is possibility of FDG uptake in benign conditions with increased glycolysis such as inflammation and granulomatous disease. Additionally, high physiological uptake within the brain, myocardium, gastrointestinal tract, urinary tract, muscle, brown fat, salivary glands, and thymus may obscure or mimic the presence of tumor deposits. Caution also is warranted in patients receiving chemotherapy in conjunction with cytokines, such as granulocyte colony stimulating factor, because these patients may have increased bone marrow FDG uptake up to 3 weeks after the last dose of cytokines (Kazama T *et al.*, 2005). Therefore, a careful evaluation of FDG-PET findings, along with a patient's accurate history and clinical examination, is necessary to minimize the number of false-positive interpretations. Another disadvantage of FDG-PET is exposure of the patient to ionizing radiation.

In conclusion, ^{18}F-FDG-PET is the imaging technique of choice for initial staging and end-of-treatment evaluation. However, ^{18}F-FDG is not specific for tumoral tissue. Several factors can make the interpretation of PET studies challenging. Chief among these factors are the variable physiological uptake of FDG by normal tissues, FDG uptake related to inflammation, occasional malignant lesions with low avidity for FDG, limited resolution of small lesions, altered biodistribution of FDG related to hyperglycemia or hyperinsulinemia, and, in particular, bone marrow activation commonly encountered in cancer patients after treatment. It should be kept in mind that also FDG-negative lymphomas exist, and a negative ^{18}F-FDG-PET cannot exclude minimal residual disease. The interpretation of PET information requires therefore a thorough understanding of the normal physiological distribution of FDG in the body, and one should always correlate PET findings with clinical and laboratory data, other imaging modalities, and/or a biopsy.

5.3 FDG-PET/CT fusion

Advances in the scanner and computer technology enabled the development of PET/CT hybrid systems with a hardware-oriented approach to image fusion. With this type of scanner, accurately registered anatomical and functional images can be acquired in a single examination, and CT data can be used for attenuation correction of PET images. Although performed in one imaging section, the two examinations are by no means performed simultaneously. Rather, it is typically for the CT scan to be performed first, and the PET scan performed immediately after the CT scan has finished (or vice versa). Obviously, any

patient motion between the PET and CT scans would lead to inaccurate attenuation correction and unreliable fusion. Several manufacturers are now offering integrated FDG-PET/CT systems combining different models of high-resolution dedicated PET scanners and multidetector-row CT scanners in line with a common imaging bed (Blodgett TM *et al*., 2007; von Schulthess GK *et al*., 2006). A computer platform (workstation) is used to reconstruct CT and PET data and create fused PET/CT images in the transaxial, coronal, and sagittal planes for interpretation. CT attenuation value and the maximum standardized uptake value are calculated at this workstation. PET/CT has been shown to increase both the accuracy of interpretation and the confidence level of the readers, and it has already been proven as an important diagnostic tool in several cancer types, including lymphomas, for initial staging, assessing prognosis, therapy monitoring, as well as detection of recurrence.

FDG-PET and CT provide functional and anatomical information, respectively. Integration of both modalities may outperform both FDG-PET alone and CT alone in initial staging and restaging of malignant lymphoma. FDG-PET/CT fusion, using a combined PET/CT scanner, allows more accurate localization of foci with increased FDG uptake than stand-alone PET, and this may reduce the problems of physiological FDG uptake being misinterpreted as pathological and false localization of disease. An additional advantage of combined PET/CT is the use of the CT images for attenuation correction of the PET emission data, which reduces whole-body scanning time to 30 minutes. This approach also provides low-noise attenuation correction factors compared with those from standard PET transmission measurements using an external radiation source, and eliminates bias from emission contamination of post-injection transmission scans (Kwee TC, Kwee RM *et al*., 2008). A pitfall of CT-based attenuation correction, however, is that the use of concentrated CT contrast agents, CT beam-hardening artifacts due to metallic implants, and physiological motion can result in the alterations of standardized uptake value in lesions or the appearance of artifactual lesions. Thus, images without attenuation correction also should be evaluated to avoid misinterpretations (Blodgett TM *et al*., 2007; von Schulthess GK *et al*., 2006). In general, integrated PET/CT without iodinated contrast material or contrast-enhanced CT without PET is used for initial staging of lymphomas. Previous study has shown that PET/CT is more sensitive and specific than contrast-enhanced CT and suggested that PET/CT performed without intravenous contrast media is sufficient for staging patients with HD and aggressive NHL (Schaefer NG *et al*., 2004). PET/CT in particular is recommended for primary diagnosis and follow-up because it is a whole-body imaging modality and provides both anatomical and metabolic information. Furthermore, PET/CT allows earlier detection of relapse than does morphological imaging with CT or MRI alone, and it is frequently used to detect relapse at follow-up of patients with lymphomas. Radiation dose is a point of concern in FDG-PET/CT fusion, although the CT portion of a PET/CT scan is usually performed at different settings than a standard diagnostic CT to decrease the radiation burden.

5.4 Whole-body magnetic resonance imaging

The high spatial resolution and excellent soft-tissue contrast make MRI an ideal tool for the detection of parenchymal and osseous lesions. However, because of long imaging time, MRI was previously used only as a tool to image limited anatomical areas of the body. Recent

improvements in MRI technology have resulted in the availability of sufficiently fast and with diagnostic image quality sequences for whole-body MRI. As a result, whole-body MRI has become feasible for staging malignancies, including malignant lymphomas (Lauenstein TC and RC Semelka, 2006). Similar to MRI of limited body regions, whole-body MRI is sensitive to susceptibility artifacts, predominantly in the thoracic region, and motion artifacts in the abdomen (breathing and peristalsis) and thorax (breathing and cardiac motion). Image acquisition under breath-holding or respiratory triggering should therefore be applied.

Several studies have shown that whole-body MRI is feasible in both adults and children, and it may play an important role in staging and follow-up of various cancers, including malignant lymphomas (Kwee TC *et al.*, 2009; Lauenstein TC and RC Semelka, 2006; Schmidt GP *et al.*, 2009). A major advantage of whole-body MRI in malignant lymphomas is the possibility of completely evaluating the spread of disease throughout the entire body, including nodal, extra-nodal, and bone marrow involvement, in one examination (Vermoolen MA *et al.,* 2011). A disadvantage of whole-body MRI is that the image quality may be inferior to that of MRI examinations of limited body regions because the former allows less time to acquire different MRI sequences and imaging planes, and generally employs a greater slice thickness and lower spatial resolution. The use of a phased-array surface coil is preferred because it provides an increased signal-to-noise ratio and spatial resolution compared with an integrated body coil. There is no standard whole-body MRI protocol for staging malignant lymphomas yet; data regarding preferred sequence and imaging plane are lacking. A commonly recommended approach for tumor staging in general is the application of fat-suppressed T1-weighted gradient echo sequences before and after the administration of intravenous gadolinium, and fat suppressed T2-weighted sequence (Figure 2). Previous studies has shown that the fluid-sensitive fat-suppressed T2-weighted short-tau-inversion-recovery (STIR) sequence is useful for the assessment of the skeletal system and the pelvis (Lauenstein TC and RC Semelka, 2006). STIR is a particularly sensitive for detecting parenchymal and bone marrow lesions, which are generally visualized as structures of high signal intensity on images acquired with this sequence (Kwee TC, Kwee RM *et al.*, 2008). However, malignant lymph nodes can not be differentiated from benign nodes on the basis of signal intensity, neither on T1- nor on T2-weighted images.

Although MRI inherently provides superior soft-tissue contrast to CT and has the potential to characterize lesions on the basis of signal characteristics, assessment of nodal involvement is still based on size criteria. General criteria for extra-nodal involvement are any signal abnormalities or mass lesions involving soft tissues, bones, parenchymal organs, and serosal cavities. MRI is superior to CT for imaging the liver, whereas CT is superior to MRI for the assessment of mediastinal and pulmonary lymphomatous lesions (Lauenstein TC and RC Semelka, 2006). In addition, CT may be more attractive than MRI in patients with reduced health status, as it is a faster study and requires less patient cooperation.

Whole-body MRI is a feasible technique for staging malignant lymphomas, and whole-body MR imaging after gadolinium contrast injection can improve contrast and may facilitate detection of nodal and extra-nodal lymphomatous lesions (Schmidt GP *et al.*, 2009). However, disadvantages of gadolinium application include increased examination time and costs, and the potential risk of developing nephrogenic systemic fibrosis in patients with renal failure (Vermoolen MA *et al.,* 2011). In contrast to CT, FDG-PET, and FDG-PET/CT fusion, MRI has the advantage of not exposing the patient to ionizing radiation, which is

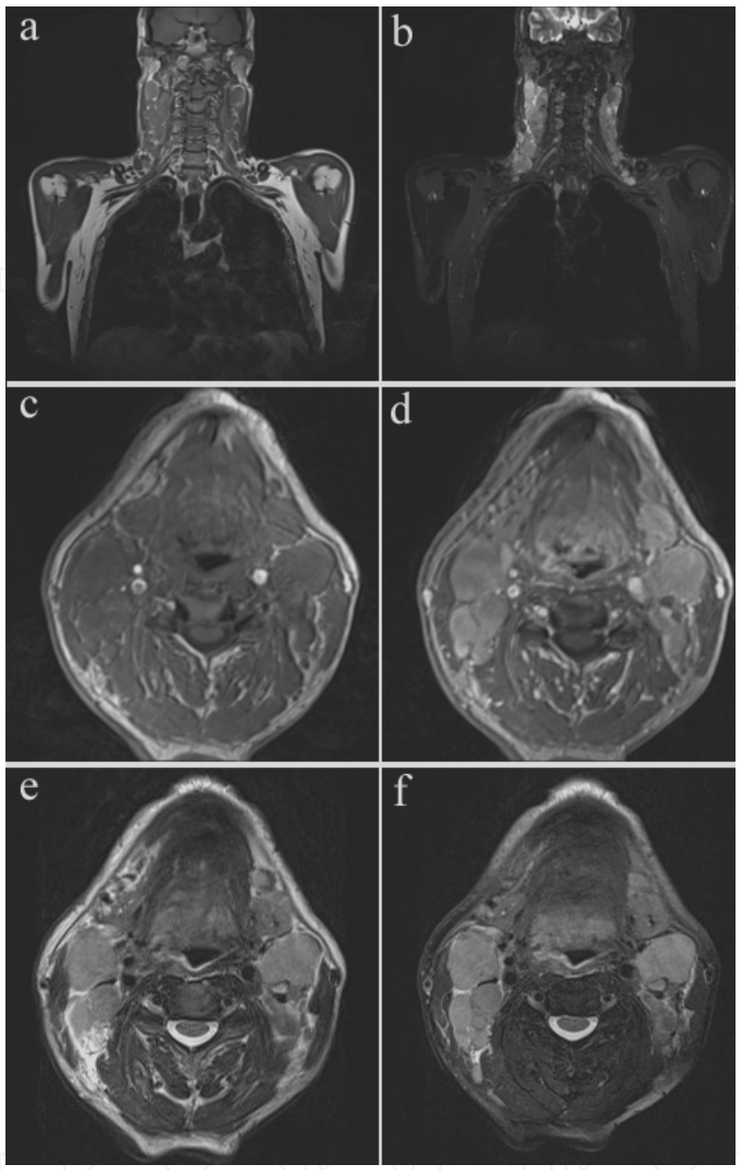

Fig. 2. MR images in a 57 year-old male patient with diffuse large B-cell lymphoma. Multiple lymph node lesions in the cervical region are shown: A coronal slice of T2-weighted image without fat-suppression (a) and the corresponding coronal slice of T2-weighted image with fat suppression (b). An axial slice of T1-weighted image before contrast agent injection and the corresponding axial slice of T1-weighted image with contrast enhancement (d). An axial slice of T2-weighted image without fat suppression (e) and the corresponding axial slice of T2-weighted image with fat suppression (f).

especially important in children. However, MRI cannot be performed in patients with pacemakers, defibrillators, or other implanted electronic devices, and in case of claustrophobia. Another limitation of conventional (anatomical) MRI is the lack of functional information, which may result in failure to detect pathological changes in normal-sized structures. However, it may be overcome with recently developed functional

MRI techniques, such as DWI. DWI highlights areas with restricted diffusion that occurs in many malignant tumors, including malignant lymphoma, without using contrast agent (Schmidt GP *et al.*, 2009; Wu X, PL Kellokumpu-Lehtinen *et al.,* 2011).

5.5 Diffusion-weighted imaging

Diffusion-weighted imaging enables the visualization of the random extra, intra, and transcellular motion of water molecules in biological tissues (Le Bihan D, 1995). DWI provides information on extracellular space tortuosity, tissue cellularity, and the integrity of cellular membranes. It can be used for the detection and characterization of pathological processes, including determination of lesion aggressiveness and monitoring response to therapy of malignant tumors, and it may therefore be of value in staging and follow-up evaluation of malignant lymphomas. The signal properties of DWI indicate both the T2 relaxation time and water diffusion, and reflect the microstructure and physiological state of tissue. Thus, subtle changes in tissue architecture can be seen by DWI. In order to create an ADC map, at least two datasets with different degrees of diffusion-weighting (i.e. *b*-values) have to be acquired. The ADC value derived from DWI is independent of the magnetic field strength and can overcome the effects of 'T2 shine-through` (an area with a very high T2 relaxation time may remain as a high signal in DWI and may be mistaken for restricted diffusion), thus allowing a more meaningful comparison of results from different studies. In general, malignant tissues tend to be hypercellular, with enlarged hyperchromatic nuclei and abundant macromolecular proteins (Wang J *et al.*, 2001). These factors reduce the diffusion space for water molecules in the extra and intracellular compartments, resulting in a decrease in ADC values (Herneth AM *et al.*, 2003; Sumi M *et al.*, 2007). In contrast, the breakdown of diffusion barriers in necrotic tissue allows the relatively unhindered diffusion of water molecules, resulting in high ADC values (Herneth AM *et al.*, 2003).

DWI using single-shot echo-planar imaging (EPI) is a well-established method to examine the brain. Extra-cranial DWI, however, did not become a clinical standard because the use of EPI was complicated by magnetic susceptibility artifacts and severe image distortion in the body (Ichikawa T *et al.*, 1998, 1999; Muller MF *et al.*, 1994). Recently introduced parallel imaging techniques, such as sensitivity encoding (Bammer R, 2003; Glockner JF *et al.*, 2005), and the development of stronger gradients and multichannel coils have largely overcome this problem; DWI of adequate quality can now be performed in the body at *b*-values of 500 - 1000 s/mm² (Koh DM and DJ Collins, 2007; Thoeny HC and F De Keyzer, 2007). Despite the above-mentioned breakthroughs in DWI, breathhold or respiratory triggered scanning was still considered necessary, since it was widely accepted that respiratory motion was an impediment for DWI of (moving) visceral organs (Low RN and J Gurney, 2007) .

DWI can be performed quickly and does not require a contrast agent. DW-MRI is not just sensitive to microscopic water movements but also to physiological motions of greater magnitude, such as blood, cerebrospinal fluid and ductal flows. At low *b*-values (< 50 - 100 s/mm²) bulk water movement will be the predominant factor determining the ADC; at higher *b*-values, bulk water motion has less a role in the continued signal attenuation. Thus, it is possible to differentiate between the contributions made by water populations of high and low mobility by varying the experimental conditions for calculation of the ADC. It is generally accepted that with the high *b*-values used on clinical scanners (up to 500 - 1000 s/mm²), ADC reflects water diffusion in the extracellular space (Patterson DM *et al.*, 2008).

The limitations of DWI include the sensitivity to artifacts (e.g. respiration and peristalsis movements), and therefore optimization is required to maximize the signal-to-noise ratio and to minimize artifacts. Above all, DWI is not specific to cancer. In order to interpret DWI correctly, both DW images and ADC maps should be evaluated with caution and compared with corresponding anatomical images when necessary.

Takahara *et al*. reported a unique concept of whole-body DWI, called "diffusion-weighted whole-body imaging with background body signal suppression" (DWIBS) (Takahara T *et al*., 2004). This technique intentionally uses free breathing scanning rather than breathholding or respiratory triggering to visualize (moving) visceral organs and their lesions. In a study comparing pre- and post-chemotherapy FDG-PET with DWIBS, Kwee *et al*. found that DWIBS has higher spatial resolution for the imaging of patients with lymphomas, although it has only limited ability to help detect mediastinal lesions (Kwee TC, T Takahara *et al*., 2008). In addition, whole-body DWI offers a high lesion-to-background contrast, making it a sensitive technique for the detection of lesions (Kwee TC *et al*., 2009). When DWIBS is added to whole-body MRI, both anatomical and functional information can be provided within a single examination. A limitation of DWIBS is that the evaluation of structures close to the heart, such as mediastinal lymph nodes and the left liver lobe, may be compromised because of signal loss and artifacts due to cardiac motion (Vermoolen MA *et al.,* 2011).

6. View to future

6.1 Novel PET tracers

The development of new tracers and smart probes are the two key points in the development of multimodality image and diagnostic imaging in future. FDG is in routine diagnostics the most commonly used tracer for lymphoma detection and therapy follow-up, but it should be kept in mind that also FDG-negative lymphomas exist. A number of new radiotracers have been developed and are under clinical evaluation, e.g. [11C]choline, [18]F-fluorothymidine (^{18}F-FLT). One characteristic of malignant cells is an increased rate of cellular proliferation. There is good evidence that ^{18}F-FLT uptake is closely correlated with cellular proliferation (Buck AK *et al*., 2006). However, high uptake in normal bone marrow and the liver may limit the sensitivity of FLT-PET for detection of extra-nodal involvement. ^{18}F-fluoride is a positron-emitting bone-seeking agent that reflects blood flow and remodelling of bone, it is also sensitive for detection of lytic and early marrow-based metastases. The instant fusion of increased ^{18}F-fluoride uptake with morphological data of CT improves the specificity in cancer patients by accurately differentiating between benign and malignant uptake sites (Even-Sapir E *et al*., 2007).

6.2 Combination of PET with other modalities than CT: PET/MRI

Among the above-mentioned imaging techniques, no single modality is perfect and sufficient to gain all the necessary information. Therefore, the combination of multiple imaging techniques can offer synergistic advantages. Multi-modal imaging can be achieved either through the combination of imaging hardware such as PET/CT, through the combination of different contrast agents, or through co-registration of images acquired with different modalities. With regard to lymphatic imaging, this leads to improved accuracy and sensitivity of lymph nodes detection. PET/CT has been matured into an important clinical

diagnostic tool. Clinical studies have shown that the combination of anatomical structures revealed from CT and the functional information from PET into one image, with high fusion accuracy, provides an advanced diagnostic tool and research platform. Although PET/CT is already an established clinical tool, it still bears some limitations. A major drawback is that CT provides only limited soft tissue contrast and exposes the studied patient to a significant radiation dose. Since PET and CT scanner are hard-wired back to back and share a common patient bed, PET/CT does not allow simultaneous data acquisition. This temporal mismatch causes image artifacts by patient movement or respiration motion between the two scans. To overcome these limitations, recent research concentrates on the combination of PET and MRI into one single machine. The goal of this development is to integrate the PET detectors into the MRI scanner which would allow simultaneous data acquisition, resulting in combined functional and morphological images with an excellent soft tissue contrast, good spatial resolution of the anatomy, and accurate temporal and spatial image fusion. Additionally, since MRI provides also functional information such as DWI, blood oxygenation level dependant (BOLD) imaging, or spectroscopy, PET/MRI could even provide multi-functional information of pathophysiological processes *in vivo*. Furthermore, the radiation dose for PET/MR will be lower than that for PET/CT, being of particular importance for repeated studies aimed to evaluate disease progression and therapy response. First experiments with PET/MRI prototypes showed promising results, indicating its great potential for clinical imaging (Shao Y *et al*., 1997; Wagenaar DJ *et al*., 2006). Multimodality imaging techniques will play a leading role in clinical applications and development of diagnostic imaging in oncology.

6.3 High field MRI and new MR contrast agent

As MRI systems operating at 1.5 T are now widely available and provide high-quality whole-body images in a reasonable acquisition time, implementation of whole-body MRI into diagnostic protocols for malignant lymphomas is expected in the near future. In particular, MRI may be expected to be suitable to replace CT for initial staging and response evaluation, as part of radiation-minimizing policies, especially in children and pregnant women. Whole-body MRI at higher field strength (3.0 T) may increase the image quality and lesion conspicuity with a reduced scan time, since it has higher signal-to-noise ratio. However, whole-body MRI at 3.0 T is more sensitive to artifacts and has not yet been proven to be diagnostically superior to whole-body MRI at 1.5 T (Schmidt GP *et al*., 2007).

Superparamagnetic iron oxide nanoparticles, which are MRI-specific lymphographic agents, are currently under investigation and can potentially play a role in staging of malignant lymphoma by identifying involved lymph nodes independent of lymph node size (Will O *et al*., 2006).

7. Conclusion

In conclusion, making the diagnosis of lymphoma often requires multiple imaging modalities, and CT is currently the most commonly used means for staging patients with malignant lymphomas. However, CT lacks functional information, which impedes identification of disease in normal-sized organs. ^{18}F-FDG-PET and hybrid FDG-PET/CT are good alternative diagnostic tools for the initial staging and treatment response assessment of

malignant lymphomas. MRI techniques such as whole-body MRI and DW-MRI may be good radiation-free alternatives to FDG-PET/CT in lymphoma patients with multiple follow-up examinations, which may be particularly relevant for children and those who are not suitable for PET/CT exams. Furthermore, in assessment of patients with non-FDG-avid lymphomas MRI could become the imaging modality of choice. However, well-designed studies are needed to validate the accuracy of whole-body MRI and DWIBS for the staging and response assessment of malignant lymphomas.

8. Take home message

- Computed tomography remains the most commonly used modality for initial staging patients with malignant lymphomas because of its widespread availability and relatively low cost.
- FDG-PET and integrated FDG-PET/CT are the established imaging modalities for initial staging and response assessment of lymphomas. Integrated PET/CT has higher diagnostic accuracy than CT and FDG-PET alone.
- Whole-body MRI and DW-MRI are emerging radiation-free alternative imaging techniques for initial staging and treatment response evaluation of lymphomas. However, large studies are needed to determine the value of whole-body MRI and DWIBS.
- MRI at 3 T and combined PET/MRI may have potential for future clinical applications.

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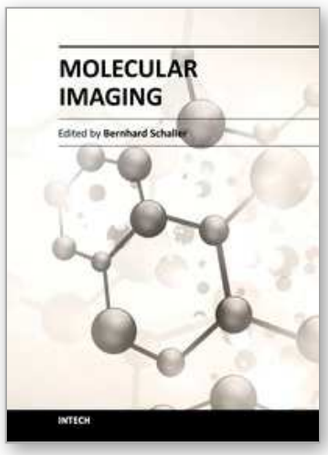

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The present book gives an exceptional overview of molecular imaging. Practical approach represents the red thread through the whole book, covering at the same time detailed background information that goes very deep into molecular as well as cellular level. Ideas how molecular imaging will develop in the near future present a special delicacy. This should be of special interest as the contributors are members of leading research groups from all over the world.

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